510K SUMMARY

AUG 2 4 2011

A.	**510(k) Number**	K110031
B.	**Purpose for Submission**	New product
D.	**Measurand**	Lupus anticoagulant
F.	**Type of Test**	Diluted Russell's venom clotting assay
H.	**Applicant**	Instrumentation Laboratory Co.
J.	**Proprietary & Established Names**	HemosIL® dRVVT Screen and HemosIL dRVVT Confirm Assays

L. Regulatory Information

1.	*Regulation section:*	21CFR §864.8950, Russell's viper venom reagent
2.	*Classification:*	Class II
3.	*Product code:*	GIR
4.	*Device classification name:*	Reagent, Russell's Viper Venom
5.	*Panel:*	81 Hematology

H. Intended Use

1. *Intended use(s):*

The HemosIL dRVVT Screen and HemosIL dRVVT Confirm assays are qualitative in-vitro diagnostic products to aid in the detection of lupus anticoagulants in human citrated plasma by the diluted Russell's Viper Venom method, on the ACL TOP® Family. The HemosIL dRVVT Screen and HemosIL dRVVT Confirm assays are intended to evaluate patients who have unexplained prolonged APTT test results The HemosIL dRVVT Screen and HemosIL dRVVT Confirm assays should be used in parallel as an integrated test for Lupus Anticoagulant detection.

2. *Indication(s) for use:*

Same

Special conditions for use statement(s):
For *in-vitro* diagnostic use only. For prescription use. HemosIL dRVVT Confirm is intended to be used in conjunction with HemosIL dRVVT Screen.

3. *Special instrument requirements:*

ACL TOP Family Analyzers

I. Device Description

DRVVT Screen and dRVVT Confirm are improved dRVVT reagents, intended to simplify and standardize the detection of Lupus Anticoagulant (LA) disorder in clinical chemistry evaluations. DRVVT Screen is poor in phospholipid, making it sensitive to LA. The additional amount of phospholipid in dRVVT Confirm neutralizes LA to give shorter clotting times.

Russell's viper venom, in the presence of calcium, directly activates factor X (in a test sample). DRVVT Screen and dRVVT Confirm are therefore unaffected by contact factor abnormalities, factor VII, VIII and IX deficiencies, or inhibitors. As a result, dRVVT Screen and dRVVT Confirm are more specific tests for the evaluation of LA than APTT.

J. Substantial Equivalence Information

1. *Predicate device name(s):* HemosIL LAC Screen & LAC Confirm (self)
2. *Predicate 510(k) number(s):* K990302
3. *Comparison with predicate:*

Similarities

The applicants, HemosIL dRVVT Screen and HemosIL dRVVT Confirm (PNs 000200301500 & 00020301600 respectively) are Substantially Equivalent to their predicates, the HemosIL LAC Screen and HemosIL LAC Confirm (K990302).

Table of similarities:

Item	Predicate Device	Applicant
Device Name	HemosIL LAC Screen & LAC Confirm	HemosIL dRVVT Screen & dRVVT Confirm
K#	K990302	K110031
Indications for Use	HemosIL LAC Screen and HemosIL LAC Confirm are *in vitro* diagnostic products for the detection of lupus anticoagulants (a type of phospholipid interfering antibody) in human citrated plasma on the ACL TOP Family.	The HemosIL dRVVT Screen and HemosIL dRVVT Confirm assays are qualitative in-vitro diagnostic products to aid in the detection of lupus anticoagulants in human citrated plasma by the diluted Russell's Viper Venom method, on the ACL TOP® Family. The HemosIL dRVVT Screen and HemosIL dRVVT Confirm assays are intended to evaluate patients who have unexplained prolonged APTT test results The HemosIL dRVVT Screen and HemosIL dRVVT Confirm assays should be used in parallel as an integrated test for Lupus Anticoagulant detection.
Sample Type	Citrated plasma	Same

Item	**Predicate Device**	**Applicant**
Reagent composition	Russell's viper venom, phospholipids, calcium and heparin inhibitor	Same
Test Principle	LAC Screen and LAC Confirm are improved dRVVT reagents, intended to simplify and standardize the detection of Lupus Anticoagulant (LA) disorder in clinical chemistry evaluations. LAC Screen is poor in phospholipid, making it sensitive to LA. The additional amount of phospholipid in LAC Confirm neutralizes LA to give shorter clotting times. Russell's viper venom, in the presence of calcium, directly activates factor X (in a test sample).	Same

Differences

The main difference between the applicant, HemosIL dRVVT Screen and dRVVT Confirm, and their predicates HemosIL LAC Screen and LAC Confirm, is that the applicants have improved stability as compared to their predicates.

K. Standard/Guidance Document Referenced (if applicable)

No performance standard or FDA guidance has been established for these reagents.

L. Test Principle

In dRVVT *screening* assays, a low, rate-limiting concentration of phospholipid is used to give a clotting time which is sensitive to the presence of lupus anticoagulants, since anti-phospholipid antibodies interfere with the clot-promoting role of phospholipid *in vitro*. A prolonged clotting time of a patient sample that does not correct with the addition of an equal volume of normal plasma suggests the presence of a lupus anticoagulant.

An abnormal result for the initial dRVVT screening assay should be followed by a dRVVT *confirmatory* test. In this test, the inhibitory effect of lupus anticoagulants on phospholipids in the dRVVT can be overcome by adding an excess of phospholipid to the assay.

The clotting times of both the initial dRVVT assay and confirmatory test are subsequently normalized and then used to determine a ratio: the time *without* phospholipid excess to time *with* phospholipid excess, the so called "normalized ratio". A ratio greater than the laboratory established cut-off is considered a positive result and implies that the patient may have anti-phospholipid antibodies.

M. Performance Characteristics

1. *Analytical performance*

a. Precision/Reproducibility

Precision was assessed utilizing 3 lots of reagent on 3 representative members of the ACL TOP Family (ACL TOP and ACL TOP 500 CTS) by 3 independent operators. Precision was evaluated in accordance with CLSI EP05-A2[13], for 20 days, with 2 runs per day and 2 replicates per run for each sample level (n=80/ instrument/ lot), with the following results:

ACL TOP Family	*dRVVT NR*
LA Negative Control	1.00
Weakly LA Positive Control	1.35
LA Positive Control	1.77

HemosIL dRVVT NR	*Within Run (%CV)*			*Between Run (%CV)*			*Total (%CV)*		
	Lot 1	Lot2	Lot3	Lot 1	Lot2	Lot3	Lot 1	Lot2	Lot3
LA Negative Control	1.2	2.0	0.8	1.7	2.8	1.9	2.3	3.4	2.1
Weakly LA Positive	1.1	0.9	0.6	2.7	2.1	2.0	3.0	2.6	2.2
LA Positive Control	1.5	0.9	1.1	4.4	3.4	2.5	5.0	3.5	3.0

b. Linearity/assay reportable range: NA, qualitative assay.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Unopened reagents are stable until the expiration date shown on the vial when stored at 2-8°C. Stability after reconstitution: 15 days at 2-8°C in the closed original vial or 3 days at 15°C in the original vials on the ACL TOP Family. dRVVT Screen/ Confirm may be used with either fresh or frozen samples. For optimal stability remove reagents from the system and store them, closed, at 2-8°C, in their original vials. Based on the results of the accelerated stability study, a shelf-life of at least 2 years is claimed for the products when stored at 2- 8°C. Real-time stability testing is ongoing, and will be used to update the shelf life as more data becomes available.

d. Detection limit: NA

e. Analytical specificity:

Interference studies were conducted on a representative member of the ACL TOP Family. Different concentrations of interferent were spiked into pooled normal plasma, weak LA Positive plasma and high LA Positive plasma The maximum concentration tolerated in the assay was defined as the highest concentration of interferent relative to the recovered value of the base clotting time ± 15%. The maximum tolerated concentrations not causing interference at any LA level tested were:

Possible Interferant	*Not affected by concentrations*
Unfractionated Heparin (UFH)	≤ 1.0 IU/mL
Low Molecular Weight Heparin (LMWH)	≤ 1.0 IU/m
Hemoglobin	≤ 200 mg/dL
Bilirubin	≤ 10 mg/dL
Triglyceride	≤ 500 mg/dL

Normalized dRVVT ratio higher than the internal-study cut-off (NR > 1.2) was found in the following plasma samples using dRVVT Screen/dRVVT Confirm:

Sample	*ACL TOP Base*	*ACL TOP 500CTS*
Known LA Positive	100% (35/35)	100% (35/35)
Oral Anticoagulants	40% (2/5)	40% (2/5)
LMWH	0% (0/5)	0% (0/5)
UFH	20% (1/5)	0% (0/5)
DIC	0% (0/5)	0% (0/5)
Factor Deficiency	0% (0/6)	0% (0/6)

f. Assay cut-off:

The Normalized Ratio cut off was determined as recommended using 40 normal healthy individual samples and calculating the Mean + 3SD. The results were obtained using a specific lot of reagent. Due to many variables which may affect results, each laboratory should establish its own NR cut off.

System	*Normalized dRVVT Ratio Cut Off*
ACL TOP	>1.2
ACL TOP 500CTS	>1.2

2. *Comparison studies:*

a. An in-house method comparison was performed in accordance with EP09-A2[14], on 115 samples (80 Normal/ 35 known LA Positive), on a representative member of the ACL TOP Family (ACL TOP Base & ACL TOP 500 CTS). The Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) were calculated with the following result(s):

Cut-Off (Mean+3SD)	*LAC NR*	*dRVVT NR*	*PPA*	*CI 95%*	*NPA*	*CI 95%*	*Overall*	*Reference*
ACL TOP	> 1.2	> 1.2	100.0% (35/35)	90.1-100.0%	100.0% (80/80)	95.4-100.0%	100% (115/115)	LAC Screen/ Confirm
ACL TOP 500 CTS	> 1.2	> 1.2	100.0% (35/35)	90.1-100.0%	100.0% (80/80)	95.4-100.0%	100% (115/115)	

Results were subsequently validated by 3 US field sites. Each site established its own cut-off, and validated that cut-off with 100+ samples, with the following result(s):

Cut-Off (Mean+3SD)	*LAC NR*	*dRVVT NR*	*PPA*	*CI 95%*	*NPA*	*CI 95%*	*Overall*	*Reference*
Site 1	> 1.2	> 1.2	92.7% (38/41)	80.6-97.5%	98.9% (91/92)	94.1- 99.8%	97% (129/133)	LAC Screen/ Confirm
Site 2	> 1.3	> 1.3	90.2% (46/51)	79.0-95.7%	98.9% (91/92)	94.1- 99.8%	95.8% 137/143	
Site 3	> 1.3	> 1.2	98.1% (52/53)	90.1-99.7%	100.0% (80/80)	95.4-100.0%	99.2% (132/133)	

b. *Matrix Comparison*

A citrate study was performed to assess the effect on the assays of collecting the blood samples in 3.8% versus 3.2% sodium citrate sample tubes. Plasma from 26 donors was collected, in parallel, in both tube types. Artificial LA-Positive samples were prepared by spiking with different amounts of β2gPI antibodies to produce a range of concentrations. Using the previously established cut-off, the dRVVT Normalized Ratios for both 3.8% and 3.2% sodium citrate sample tubes were calculated. The two NRs were compared for their Positive and Negative Percent Agreement.

Results showed that the dRVVT Normalized Ratio on the ACL TOP is not affected by the type of citrate tubes used to draw blood samples.

3.8 v. 3.2% Na Citrate	*PPA*	*CI 95%*	*NPA*	*CI 95%*
ACL TOP	19/19 (100%)	83.2-100%	24/26 (92%)	75.9-97.9%

A fresh v. frozen study was conducted to demonstrate that that the results of fresh and frozen and once thawed samples are equivalent. Blood samples were drawn from 26 normal healthy donors. LA-Positive samples were prepared by spiking this pool with different amounts of β2gPI antibodies. Fresh samples were kept at room temperature. Frozen samples were stored at -65°C for 24 hr, prior to being thawed and analyzed at room temperature. Using the previously established cut-off, the dRVVT Normalized Ratios for both fresh and frozen (normal and LA-antibodies-spiked) samples were calculated. The two NRs were compared for their Positive and Negative Percent Agreement. The method comparison demonstrated that the dRVVT Normalized Ratio on the ACL TOP Family is not affected by whether the analysis is performed on fresh or frozen samples.

Fresh vs. Frozen	*PPA*	*CI 95%*	*NPA*	*CI 95%*
ACL TOP	28/28 (100%)	87.9% -100%	26/26 (100%)	87.1% -100%

3. *Clinical Studies:*
   a. *Clinical Sensitivity:* NA
   b. *Clinical Specificity:* NA
   c. *Other clinical supportive data (when a. and b. are not applicable):* NA

4. *Clinical cut-off:* NA

5. *Expected values/Reference range:*

A normal range study (n=120) was performed, in accordance with CLSI C28-A3[1], using dRVVT Screen/dRVVT Confirm on representative members of the ACL TOP Family. The following Reference intervals were established for dRVVT Screen, and for the dRVVT Screen/ Confirm Normal Ration (NR):

	Normal Ratio Reference Interval (NR)	
System	*Lower Limit*	*Upper Limit*
ACL TOP	0.92 (0.91-0.93)	1.11 (1.10-1.15)
ACL TOP 500 CTS	0.91 (0.89-0.92)	1.13 (1.11-1.16)

N. Proposed Labeling

The labeling is sufficient and satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

P. Administrative Information

Applicant Contact Information

Name of applicant:	Instrumentation Laboratory Co.
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Fax #:	781-861-4207
E-mail address:	jemery@ilww.com
Contact:	Jacqueline Emery, BSEE Regulatory Affairs Manager
Date Prepared	July 30, 2011

Reference(s):

1. CLSI C28-A3: *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory,* 3rd edition.
2. Pengo V et al. Update of the Guidelines for Lupus Anticoagulant Detection. J. Thromb. Haem. 2009; 7:1737-1740.
3. Clinical and Laboratory Standards/CLSI. Establishment of Precision of Quantitative Measurement Procedures; Approved Guideline. Document EP5-A3: Vol. 0 No. 0.
4. Clinical and Laboratory Standards/CLSI. Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline. Document EP9-A2: Vol. 22 No.19.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Instrumentation Laboratory Co.
c/o Ms. Jacqueline Emery
Regulatory Affairs Manager
180 Hartwell Road
Bedford, MA 01730

AUG 24 2011

Re: k110031
Trade/Device Name: HemosIL® dRVVT Screen and dRVVT Confirm
Regulation Number: 21 CFR 864.8950
Regulation Name: Russell Viper Venom Test
Regulatory Class: Class II
Product Code: GIR, GGC
Dated: August 16, 2011
Received: August 19, 2011

Dear Ms. Emery:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket

requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Maria M. Chan

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indications for Use Statement

510(k) Number (if known): K110031

Device Name: HemosIL® dRVVT Screen and HemosIL® dRVVT Confirm

Indications for Use:

The HemosIL dRVVT Screen and HemosIL dRVVT Confirm assays are qualitative in-vitro diagnostic products to aid in the detection of lupus anticoagulants in human citrated plasma by the diluted Russell's Viper Venom method, on the ACL TOP® Family. The HemosIL dRVVT Screen and HemosIL dRVVT Confirm assays are intended to evaluate patients who have unexplained prolonged APTT test results The HemosIL dRVVT Screen and HemosIL dRVVT Confirm assays should be used in parallel as an integrated test for Lupus Anticoagulant detection.

Prescription Use ✓ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K110031